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MATERNAL DEATHS DUE TO ECLAMPSIA AND HELLP SYNDROME: A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Hypertensive disorders in pregnancy affect 10 % of women and are a main cause of maternal morbidity and mortality worldwide. Preeclampsia, eclampsia, and Hemolysis, Elevated Liver Enzyme Levels and Low Platelet Levels (HELLP) syndrome are life-threatening hypertensive conditions that occur in pregnant woman.*

The aim: *This study aims to show maternal deaths due to eclampsia and HELLP syndrome.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 39 articles, whereas the results of our search on SagePub brought up 106 articles. The results of the search conducted for the last year of 2013 yielded a total 25 articles for PubMed and 50 articles for SagePub. The result from title screening, a total 10 articles for PubMed and 22 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *The higher maternal age; prenatal history of hypertension and hypoproteinemia; and conditions requiring oral prednisolone, oral anticoagulants, and oral antiplatelets were identified as significant risk factors underlying critical obstetric bleeding, together with other obstetric complications. Prenatal hypertension may predispose patients to HELLP syndrome, eclampsia, and subsequent development of critical bleeding, but it may not predispose the patients to atonic bleeding.*

Keyword: *HELLP, eclampsia, maternal, hypertension.*

INTRODUCTION

Preeclampsia, eclampsia, and Hemolysis, Elevated Liver Enzyme Levels and Low Platelet Levels (HELLP) syndrome are life-threatening hypertensive conditions that occur in pregnant woman. Preeclampsia is a multisystem disorder which complicates 3%–8% of all pregnancies. The diagnostic criteria of preeclampsia include (1) systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions at least 4 h apart and (2) proteinuria ≥300 mg/day in a woman with a gestational age of >20 weeks with previously normal blood pressures. Severe hypertension or signs/symptoms of end-organ injury are considered to be the severe spectrum of the disease. Eclampsia is defined as a convulsive episode or altered level of consciousness occurring in the setting of preeclampsia, provided that there is no other cause of seizures. HELLP syndrome is a life-threatening condition frequently associated with severe preeclampsia-eclampsia and is characterized by three hallmark features of hemolysis, elevated liver enzymes, and low platelets. Some researchers classify HELLP syndrome as part of microangiopathic hemolytic anemias including thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. HELLP syndrome occurs in about 0.5%–0.9% of all pregnancies and in 10%–20% of pregnancies complicated by severe preeclampsia.[1]

Following a detailed history and physical exam, patients who present with signs and symptoms of preeclampsia should undergo timely diagnostic testing. This includes pregnancy-induced hypertension laboratory testing, consisting of a urinalysis to evaluate the presence of proteinuria (either with a urine dipstick result of 2+ or greater if other methods are not readily available, a 24-hour urine collection sample significant for 300mg or greater, or a urine protein to creatinine ratio significant for 0.3 or greater), complete blood count to evaluation for thrombocytopenia (defined as a platelet count of less than 100 K/mm), a complete metabolic panel to assess for impaired liver function (with liver enzymes greater than two times the upper limit of normal), and renal insufficiency (defined as a serum concentration of 1.1 mg/dL or greater, or levels two times greater than baseline). All abnormal laboratory findings must exclude any preexisting aberrations or secondary causes for abnormalities in order to be significant for diagnosis.[2]

The etiology of HELLP syndrome is unclear but is thought to be a systemic inflammatory disorder mediated by a complement cascade. It is proposed that there may be an overlap with similar pathogenesis as in preeclampsia with poor placentation, but for unknown reasons, it can lead to exaggerated activation of the complement system and greater hepatic inflammation in patients with HELLP syndrome. A subset of HELLP syndrome is caused by complement dysregulation associated with thrombotic microangiopathy and can present with pregnancy-related hemolytic uremic syndrome (HUS). Fetal long-chain 3-hydroxy acyl CoA dehydrogenase deficiency (LCHAD) may be contributing to the pathogenesis of HELLP syndrome, but evaluation for these genetic variants is unnecessary as there is no identified role in clinical management,[3]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of the maternal deaths due to eclampsia and HELLP syndrome. It is possible to accomplish this by researching or investigating maternal deaths due to eclampsia and HELLP syndrome. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the maternal deaths due to eclampsia and HELLP syndrome. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " Maternal deaths due to eclampsia and HELLP syndrome" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("HELLP"[MeSH Subheading] OR "HELLP syndrome"[All Fields] OR "Incident of HELLP syndrome [All Fields]) AND ("Eclampsia"[All Fields] OR " HELLP syndrome during pregnancy"[All Fields]) AND ("Complications of eclampsia"[All Fields]) OR ("Complication of HELLP syndrome [All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as

sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

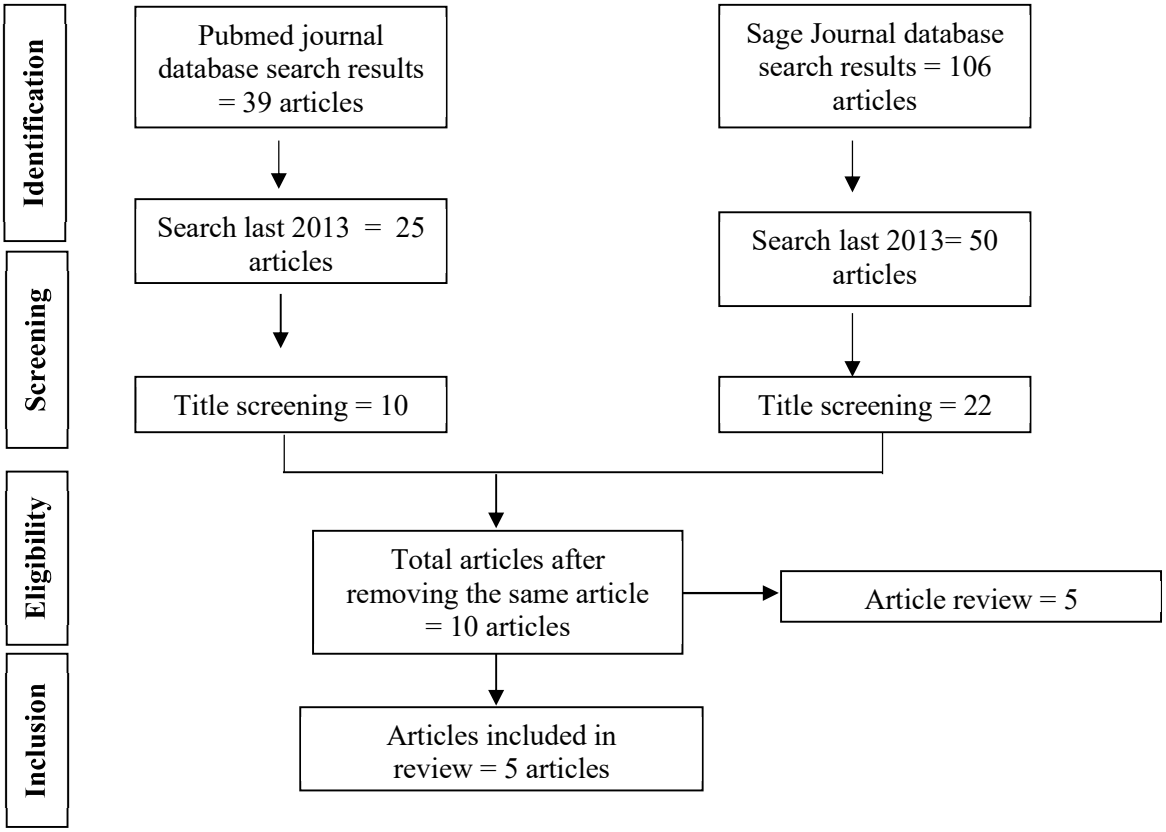

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 39 articles, whereas the results of our search on SagePub brought up 106 articles. The results of the search conducted for the last year of 2013 yielded a total 25 articles for PubMed and 50 articles for SagePub. The result from title screening, a total 10 articles for PubMed and 22 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Gracia, PV *et al* (2015)[4] showed Eclampsia with HELLP syndrome is a dangerous complication associated with pregnancy. Low platelet count secondary to HELLP syndrome and severe systolic hypertension were independently associated with maternal mortality from eclampsia.

Panda, S *et al* (2021)[5] showed Routine antenatal screening for HDP in all pregnant women with appropriate and timely interventions in women at risk may help reduce HDP-related maternal and perinatal morbidity and mortality.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Gracia, PV *et al* ., 2015[4]	America	A cross-sectional study	196 patients	There were 196 eclampsia cases among 115 038 deliveries; 142 (72.4%) women had eclampsia alone and 54 (27.6%) women had concomitant HELLP syndrome. Severe systolic hypertension (≥160 mm Hg), severe diastolic hypertension (≥110 mm Hg), and hypertensive encephalopathy were significantly more common among women with HELLP than among those with eclampsia alone (P = 0.01 for all). There were 8 (4.1%) maternal deaths, all in the group with HELLP syndrome, and 18 (9.1%) perinatal deaths. In a multivariate regression model, maternal mortality was significantly associated with low platelet count and severe systolic hypertension (P b 0.05).
Panda, S *et al.*, 2021[5]	India	A prospective cross-sectional study	5460 participants	In our study, out of 5460 deliveries, 402 (7.4%) cases had HDP, 27.6% had gestational hypertension, 27.6% had mild preeclampsia, 33.6% had severe preeclampsia, and 11.2% had eclampsia. Fifty-four (13.4%) cases required admission in the intensive care unit and 12 (2.9%) ended in maternal deaths. The cause of maternal mortality was cerebral hemorrhage in eight (66.6%) cases and pulmonary edema in four (33.3%) cases. All maternal deaths occurred in women with severe preeclampsia and eclampsia and eclampsia was significantly higher. Maternal deaths were more when systolic blood pressure (SBP) was ≥ 160mmHg, diastolic blood pressure (DBP) was ≥ 110mmHg, significantly more with 3+ proteinuria, but no association was found with age, parity, booking status, socio-economic status, gestational age, or mode of delivery. All mothers with HDP received treatment with antihypertensives. There were

				60 (14.9%) cases of perinatal mortality. Perinatal deaths were more in unbooked cases and preterm HDP, significantly more with SBP ≥160 mmHg, DBP ≥110 mmHg and ≥2+proteinuria, but no association was found with parity or mode of delivery. Besides mortality, there was a significant burden of maternal and perinatal morbidity, which was more in women with severe preeclampsia and eclampsia.
Zanette, E *et al*., 2014[6]	Brazil	A cross-sectional, multicenter study	6707 women	Severe hypertensive disorders were the main cause of severe maternal morbidity (6706/9555); the prevalence of near miss was 4.2 cases per 1000 live births, there were 8.3 cases of Near Miss to 1 Maternal Death and the mortality index was 10.7% (case fatality). Early onset of the disease and postpartum hemorrhage were independent variables associated with severe maternal outcomes, in addition to acute pulmonary edema, previous heart disease and delays in receiving secondary and tertiary care.
Lisonkova, S *et al*., 2020[7]	America	A retrospective population-based cohort study.	2663 participants	The incidence of HELLP syndrome was 2.5 per 1000 singleton deliveries (n = 2663). Risk factors included: age ≥35 years, rural residence, nulliparity, parity ≥4, pre-pregnancy and gestational hypertension and diabetes, assisted reproduction, chronic cardiac conditions, systemic lupus erythematosus, obesity, chronic hepatic conditions, placental disorders (e.g. fetomaternal transfusion) and congenital anomalies. PROM and age
Mooij, R *et al*., 2015[8]	Tanzania	A retrospective study	3398 women	. Of the 3398 women who gave birth in the hospital 26 cases of severe pre-eclampsia and 55 cases of eclampsia were diagnosed (0.8 and 1.6 %). Six women with eclampsia died (case fatality rate 11 %). Convulsions in patients with eclampsia were classified as antepartum (44 %), intrapartum (42 %) and postpartum (15 %). Magnesium was given in 100 % of patients with eclampsia and was effective in

				controlling convulsions. Intravenous antihypertensive treatment was only started in 5 % of patients. Induction of labour was done in 29 patients (78 % of women who were not yet in labour). Delivery was spontaneous in 67 %, assisted vaginal (ventouse) in 14 % and by Caesarean section in 19 % of women. Perinatal deaths occurred in 30 % of women with eclampsia and 27 % of women with severe pre-eclampsia and were associated with low birth weight and prolonged time between admission and birth.

Zanette, E *et al* (2014)[6] showed In women with severe hypertensive disorders, the current study identified situations independently associated with a severe maternal outcome, which could be modified by interventions in obstetric care and in the healthcare system. Furthermore, the study showed the feasibility of a hospital system for surveillance of severe maternal morbidity.

Lisonkova, S *et al* (2020)[7] showed This large population-based study shows that HELLP syndrome is a severe complication of pregnancy and is strongly associated with severe adverse maternal and fetal/ infant outcomes. Besides the known risk factors of advanced maternal age, nulliparity, hypertensive disorders, obesity, and assisted reproduction, we also observed strong associations with high parity (≥4 prior births), rural residence, pre-pregnancy and gestational diabetes, systemic lupus erythematosus, placental disorders, chronic hepatic conditions and congenital anomalies. Contemporary surveillance of high-risk pregnancies does not specifically address women at risks of HELLP syndrome, but rather includes all women with hypertensive disorders who are at risk of pre-eclampsia in general. This was an exploratory study. Further research is required to refine our findings and determine whether HELLP syndrome at term can be successfully predicted and prevented by early delivery in women with specific chronic conditions or pregnancy complications that place them at high risk for the syndrome.

Mooij, R *et al* (2015)[8] showed The CFR of eclampsia was 11 % and the perinatal mortality 30 % in this rural hospital. Longer admission to delivery intervals were not associated with maternal mortality. Foetal death is associated with low birth weight and prolonged time between admission and birth. Better outcomes could be achieved by better treatment of hypertension and starting induction of labour as soon as possible (after stabilising the condition of the mother). Reliable protein measurements should be available for accurate diagnosis. Most women gave birth vaginally after induction of labour with misoprostol. This practice of first stabilising maternal condition and then opting for a vaginal birth has proven to be safe, even in those who eventually needed a CS.

DISCUSSION

Hypertensive disorders of pregnancy (HDP) represent a major cause of pregnancy-associated morbidity and mortality. These disorders have far-reaching consequences that extend well beyond the pregnancy and the immediate postpartum period. According to the Centers for Disease Control (CDC), HDP, including preeclampsia, accounts for nearly 7% of all maternal deaths. HDP consists of a myriad of diagnoses, including chronic hypertension, gestational hypertension, preeclampsia, preeclampsia with severe features, and eclampsia. Similar to chronic hypertension, data suggest that preeclampsia has significant sequelae later in life. Therefore, a thorough understanding of the pathogenesis and prediction of HDP and its implications on short- and long-term health outcomes is crucial to provide optimal care to pregnant patients, especially as they transition out of the immediate postpartum period.[9]

To improve long-term morbidity in the pregnant patient, minimizing the development of disease and early detection are paramount. No perfect prediction model exists to identify all patients who will develop HDP accurately nor define those at greatest risk of long-term morbidity. However, risk factors for the disease have been identified. As determined by the American College of Obstetrics and Gynecology (ACOG), risk factors for the development of preeclampsia include prior preeclampsia, chronic hypertension, diabetes, renal disease, autoimmune diseases such as lupus, and multifetal gestations. Traditionally, the Black race has been identified as a risk factor for the development of HDP, with Black people having much higher rates of preeclampsia compared to White counterparts. Recent research into health inequities, however, has questioned whether one's race or ethnicity is a concrete risk factor for HDP or whether race and ethnicity are merely reflective of unequal access to care and unfavorable socio-economic conditions present in the healthcare system and society.[9]

Critical bleeding in obstetrics is a major cause of maternal death during pregnancy worldwide, accounting for approximately 300,000 deaths globally. With advances in obstetric critical care and treatment over the last several decades, maternal mortality has significantly decreased. However, some women still lose their lives during childbirth because of miscellaneous complications like critical bleeding, intracranial hemorrhage, and sepsis. Among these, maternal death due to critical bleeding decreased by approximately 50% between 2010 and 2020 in the country. This reduction could be partly attributed to the "Guidelines for management of critical bleeding in obstetrics," published by Japan Society of Obstetrics and Gynecology and other four related academic societies in 2010. This guideline emphasized the difficulty in accurately measuring the amount of bleeding during childbirth and incorporated an estimator of blood loss based on vital signs, namely, the Shock Index (SI) calculated as the heart rate divided by the systemic blood pressure. An SI > 1.5 implies the presence of critical blood loss of >2500 cc, which is a life-threatening condition and is considered as critical bleeding in obstetrics. Although the possibility of overtriage exists in implementing this criterion, the guidelines could have contributed to reducing maternal death in the last decade in Japan. Many obstetric conditions are known risk factors for critical bleeding, such as amniotic embolism, uterine rupture, placental abruption, atonic bleeding, placenta accreta, and uterine inversion.[10]

The clinical and laboratory manifestations of HELLP syndrome and preeclampsia-eclampsia differ; however, these two conditions are considered to fall within obstetric hypertensive disorders. HELLP syndrome, preeclampsia-eclampsia, and HDP are all considered to result from vascular dysfunction, such as widespread vasospasm caused by multi-organ endothelial vascular damage in different organs or systems, during pregnancy.[10]

CONCLUSION

The higher maternal age; prenatal history of hypertension and hypoproteinemia; and conditions requiring oral prednisolone, oral anticoagulants, and oral antiplatelets were identified as significant risk factors underlying critical obstetric bleeding, together with other obstetric complications. Prenatal hypertension may predispose patients to HELLP syndrome, eclampsia, and subsequent development of critical bleeding, but it may not predispose the patients to atonic bleeding. Mothers with these obstetric and non-obstetric risks of critical bleeding may benefit from additional caution to avoid overlooking persistent bleeding, and to ensure swift interventions with efficient transfusion therapy, hemostatic procedures, and damage control surgeries.

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